## 2nd Revised 256-152div corrected in response to notice to comply.txt SEQUENCE LISTING



```
<110> YOUNG, ANDREW A.
VINE, WILL
BEELEY, NIGEL R.A.
PRICKETT, KATHRYN S.
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<120> INOTROPIC AND DIURETIC EFFECTS OF GLP-1 AND GLP-1 AGONISTS

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<130> 256-152DIV US
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<140> 10/656,093

<141> 2003-09-05

<160> 75

<170> PatentIn Ver. 2.1

<210> 1

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<212> PRT

<213> Heloderma horridum

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<223> Exendin-3

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Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser 20 25 30

Ser Gly Ala Pro Pro Pro Ser

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Ser Gly Ala Pro Pro Pro Ser

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<223> GLP-1

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<222> (9)
<223> Asp or Glu
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<223> Ala, Leu, Ile, Val, pentylglycine or Met
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2nd Revised 256-152div corrected in response to notice to comply.txt
     are Ala; and the compound is not exendin-3 or exendin-4
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2nd Revised 256-152div corrected in response to notice to comply.txt
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Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
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2nd Revised 256-152div corrected in response to notice to comply.txt Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn 20 25 <210> 17 <211> 28 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: Exendin or GLP-1 agonist <220> <223> C-term amidated <400> 17 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala Glu 1 5 10 15Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn <210> 18 <211> 28 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: Exendin or GLP-1 agonist <220> <223> C-term amidated <400> 18 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Ala 1 5 10 15 Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn 20 25 <210> 19 <211> 28 <212> PRT <213> Artificial Sequence <220> <223> Description of Artificial Sequence: Exendin or GLP-1 agonist <220> <223> C-term amidated <400> 19 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn

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2nd Revised 256-152div corrected in response to notice to comply.txt
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Ser Gly Ala Pro Pro Pro
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<sup>&</sup>lt;210> 29

<sup>&</sup>lt;211> 38

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2nd Revised 256-152div corrected in response to notice to comply.txt
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Ser Gly Ala Pro Pro Pro 35

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Ser Gly Ala Pro Pro 35

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**∠**400\ 31

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Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser 20 25 30

Ser Gly Ala Pro Pro

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                                       10
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20 25 30
                                         Page 14
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20 25 30
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2nd Revised 256-152div corrected in response to notice to comply.txt
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His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
20 25 30
Ser Gly Ala Xaa Xaa
35
<210> 52
<211> 36
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<221> MOD_RES
<222> (31)
<223> hPro
<220>
<221> MOD_RES
<222> (36)
<223> hPro
<220>
<223> C-term amidated
<400> 52
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser 20 25 30
ser Gly Ala Xaa
<210> 53
<211> 35
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2nd Revised 256-152div corrected in response to notice to comply.txt
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
Arg Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala
<210> 54
<211> 30
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220> -
<223> C-term amidated
<400> 54
His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly 25 30
<210> 55
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<221> MOD_RES
<222> (6)
<223> Naphthylala
<220>
<223> C-term amidated
<400> 55
His Gly Glu Gly Thr Xaa Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu 1 5 15
Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
                                         Page 22
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<210> 56
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
<400> 56
His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn 20 25
<210> 57
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu Glu 1 5 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25
<210> 58
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
<400> 58
His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Ala Glu 1 	 5 	 10 	 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25
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2nd Revised 256-152div corrected in response to notice to comply.txt
<210> 59
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<221> MOD_RES
<222> (10)
<223> pentylgly
<220>
<223> C-term amidated
<400> 59
His Gly Glu Gly Thr Phe Thr Ser Asp Xaa Ser Lys Gln Leu Glu Glu
Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn 20 25
<210> 60
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
     GLP-1 agonist
<220>
<221> MOD_RES
<222> (22)
<223> Naphthylala
<220>
<223> C-term amidated
<400> 60
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
Glu Ala Val Arg Leu Xaa Ile Glu Phe Leu Lys Asn
<210> 61
<211> 28
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<221> MOD_RES
<222> (23)
<223> tButylgly
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2nd Revised 256-152div corrected in response to notice to comply.txt
<220>
<223> C-term amidated
<400> 61
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
Glu Ala Val Arg Leu Phe Xaa Glu Trp Leu Lys Asn
20 25
<210> 62
<211> 28
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
<400> 62
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
                                      10
Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn
<210> 63
<211> 33
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<223> C-term amidated
<400> 63
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu 1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
Ser
<210> 64
<211> 29
<212> PRT
<213> Artificial Sequence
<220>
<223> Description of Artificial Sequence: Exendin or
      GLP-l agonist
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2nd Revised 256-152div corrected in response to notice to comply.txt
<220>
<223> C-term amidated
<400> 64
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly
20 25
<210> 65
<211> 37
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: Exendin or
      GLP-1 agonist
<220>
<221> MOD_RES
<222> (31)
<223> hPro
<220>
<221> MOD_RES
<222> (36)..(37)
<223> hPro
<220>
<223> C-term amidated
<400> 65
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser 20 25 30
Ser Gly Ala Xaa Xaa
35
<210>
       66
<211>
       29
<212>
       PRT
<213>
       artificial sequence
<220>
<223> Agonist of GLP-1
<220>
<221>
<222>
       MOD_RES
       (1)..(1)
       Ala is modified with an R group which can be 4-imidazopropionyl
<223>
       (des-amino-histidyl), 4-imidazoacetyl, or 4-imidazo-a,
```

adimethyl-acetyl

MOD\_RES

<220> <221>

```
2nd Revised 256-152div corrected in response to notice to comply.txt
<222>
       (19)..(19)
<223>
       Xaa is a Lys or Arg
<220>
       MOD_RES
<221>
<222>
       (27)..(27)
       Lys is modified with an R group consisting of C6 -C10 unbranched
       acyl, or is absent
<220>
<221>
       MOD_RES
<222>
       (29)..(29)
<223>
       Arg is modified with an R group consisting of Gly-OH or NH2
<400> 66
Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly Gln
Ala Ala Xaa Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
<210>
       67
       19
<211>
<212>
       PRT
<213>
       artifical sequence
<220>
<221>
       MOD_RES
<222>
       (1)..(1)
<223>
       Ser is modified by H2N, H2N-Ser, H2N-Val-Ser, H2N-Asp-Val-Ser. or
       any one of SEQ ID NO:68 to 74
<220>
<221>
       MOD_RES
<222>
       (17)..(17)
<223>
       Xaa is a Lys or Arg.
<220>
<221>
       MOD_RES
<222>
       (19)..(19)
       Arg can be modified by the group consisting of NH2, OH, Gly-NH2,
<223>
       or Gly-OH
<400> 67
Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
Xaa Gly Arg
<210>
       68
<211>
       4
<212>
       PRT
       artificial sequence
<213>
```

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2nd Revised 256-152div corrected in response to notice to comply.txt
<220>
       variable sequence insert for artificial GLP-1 analog
<223>
<400>
       68
Ser Asp Val Ser
<210>
       69
<211>
      5
<212> PRT
<213> artificial sequence
<220>
<223>
       variable sequence insert for artificial GLP-1 analog
<400>
       69
Thr Ser Asp Val Ser
<210>
       70
<211>
<212>
       6
       PRT
<213>
       artificial sequence
<220>
<223>
       variable sequence insert for artificial GLP-1 analog
<400> 70
Phe Thr Ser Asp Val Ser
<210> 71
<211>
<212> PRT
<213>
       artificial sequence
<220>
<223>
       variable sequence insert for artificial GLP-1 analog
<400>
       71
Thr Phe Thr Ser Asp Val Ser
1 5
       72
<210>
<211>
       8
<212>
      PRT
<213> artificial sequence
<220>
<223>
       variable sequence insert for artificial GLP-1 analog
<400>
       72
Gly Thr Phe Thr Ser Asp Val Ser
                                       Page 28
```

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2nd Revised 256-152div corrected in response to notice to comply.txt
1
<210>
      73
<211>
       9
<212>
       PRT
<213>
       artificial sequence
<220>
<223>
      variable sequence insert for artificial GLP-1 analog
<400>
      73
Glu Gly Thr Phe Thr Ser Asp Val Ser
<210>
       74
<211>
       10
<212>
       PRT
<213>
       artificial sequence
<220>
<223>
      variable sequence insert for artificial GLP-1 analog
<400>
       74
Ala Glu Gly Thr Phe Thr Ser Asp Val Ser
1 5 10
<210>
       75
<211>
       29
<212>
       PRT
<213>
      artificial sequence
<220>
<223>
      artificial
<220>
<221>
       MOD_RES
<222>
       (1)..(1)
       neurtal amino acid or D or N-acylated or alkylated form of
<223>
       histidine can be substituted for His
<220>
<221>
       MOD_RES
<222>
       (2)..(2)
<223>
       small neutral amino acid can be substituted for Ala
<220>
<221>
       MOD_RES
<222>
<223>
       acidic or neutral amino acid can be substituted for Glu
<220>
<221>
       MOD_RES
<222>
       (4)..(4)
<223>
       neutral amino acid can be substituted for Gly
<220>
<221>
      MOD_RES
                                        Page 29
```

```
2nd Revised 256-152div corrected in response to notice to comply.txt
<222>
<223>
       acidic amino acid can be substituted for Asp
<220>
<221>
       MOD_RES
<222>
       (10)..(10)
<223>
       Tyr can be substituted for Val
<220>
<221>
       MOD_RES
<222>
       (12)..(12)
<223> Lys can be substituted for Ser
<220>
<221>
<222>
<223>
       MOD_RES
       (15)..(15)
       Asp can be substituted for Glu
<220>
<221>
<222>
       MOD_RES
       (16)..(16)
<223>
       Ser can be substituted for Gly
<220>
<221>
<222>
       MOD_RES (17)..(17)
<223>
       Arg can be substituted for Gln
<220>
<221>
       MOD_RES
<222>
       (18)..(18)
<223> Arg can be substituted for Ala
<220>
<221>
<222>
       MOD_RES
       (20)..(20)
<223>
       Lys can be substituted for a neutral amino acid, arg, or a D form
       of lys
<220>
<221>
       MOD_RES
<222>
       (20)..(20)
<223>
       Gln can be substituted for Lys
<220>
<221> MOD_RES
<222>
       (25)..(25)
<223>
       Trp can be substituted for an oxidation-resistant amino acid
<220>
<221>
<222>
       MOD_RES
       (28)..(28)
       Lys can be substituted for a neutral amino acid, arg, or a D form of lys
<223>
<220>
<221>
       MOD_RES
<222>
       (29)..(29)
       Xaa is a Gly, Gly-Arg, Gly-Arg-Gly, or absent
<223>
<400> 75
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2nd Revised 256-152div corrected in response to notice to comply.txt His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly 1 5 15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Xaa 20 25